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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/435,403 | 11/05/1999 | JOHN S. LOLLAR | 88-98 | 5191 |

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| EXAMINER | |
|---|---|
| SCHNIZER, HOLLY G | |
| **ART UNIT** | **PAPER NUMBER** |
| 1653 | 7 |

DATE MAILED: 12/10/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

FILE COPY

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/435,403 | LOLLAR, JOHN S. | |
| | Examiner | Art Unit | |
| | Holly Schnizer | 1653 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

**Status**

1)☒ Responsive to communication(s) filed on *28 March 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-3* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-3* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

**Attachment(s)**

14) ☒ Notice of References Cited (PTO-892)
15) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
16) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
17) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
18) ☐ Notice of Informal Patent Application (PTO-152)
19) ☒ Other: *See Continuation Sheet* .

Continuation of 19. Other: Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

# NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- [ ] 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).
- [X] 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- [X] 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- [ ] 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."
- [ ] 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- [ ] 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- [ ] 7. Other: _

## Applicant Must Provide:

- [X] An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
- [X] An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.
- [x] A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g).

For questions regarding compliance to these requirements, please contact:

- For Rules Interpretation, call (703) 308-4216 or (703) 308-2923
- For CRF Submission Help, call (703) 308-4212
- For PatentIn software Program Support:
  - HELP DESK: (703) 739-8559, ext 508, M-F, 8 AM to 5 PM EST except holidays
  - Email: PATIN21HELP@uspto.gov
  - To purchase PatentIn sofftware: (703) 306-2600

**PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR RESPONSE**

## DETAILED ACTION

### Status of the Claims

1. The Response filed September 24, 2001 (Paper No. 6) has been entered and considered. Claims 2 and 3 have been added. Therefore, Claims 1-3 are pending.

### *Sequence Listing*

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) before the application can be further examined under 35 U.S.C. §§ 131 and 132.

3. In response to this Office Action, Applicant must comply with the sequence rules, 37 CFR 1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). Direct the reply to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the reply.

4. The specification refers to SEQ ID NOs: 1 and 2 on page 4. However, a paper copy or computer readable form of the sequence listing is not present in the application.

***Rejections Withdrawn***

***5.*** The rejection of Claim 1 under 35 U.S.C. 103(a) as being unpatentable over Gething et al. (U.S. Patent No. 5,041,376; issued 1991) in view of Lollar (U.S. Patent No. 5,859,204; filing date 1996; submitted in IDS filed 3-28-00 as Paper No. 4) is withdrawn in view of the lack of enablement rejection below. Upon consideration of the arguments and references found in an updated search, it appears that, at the time of the invention, the need for a factor VIII molecule that would evade the immune system was recognized, the factor VIII epitopes for inhibitory antibodies had been characterized, and the practice of inserting N-glycosylation sites into proteins to shield epitopes from immune recognition was standard practice. However, upon consideration of a reference discovered in an updated search of the art, it appears that the effect of the mutation to make the glycosylation site and the glycosylation site itself on protein function is highly unpredictable. Therefore, since Gething et al. and Lollar et al. do not teach specific positions in the factor VIII molecule where a glycosylation site may be inserted to result in a factor VIII protein that maintains function, the claim does not appear to be obvious.

***New Rejections***

***Claim Rejections - 35 USC § 112***

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for preparing a factor VIII molecule having modified glycosylation wherein a specific mutation at the A2 domain of a factor VIII protein is made specifically by replacing leucine 486 of SEQ ID NO: 2 with asparagine, does not reasonably provide enablement for a method for preparing a factor VIII protein having modified glycosylation comprising making a mutation anywhere in the protein sequence, or anywhere in the A2 or C2 domains to insert a glycosylation site. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

8. The factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. In the present case, it appears that undue experimentation would

be required to practice the claimed method to successfully produce a functional factor VIII protein having the structural limitations of the claims.

9. The claims are broadly drawn to a method of making a mutation anywhere in the factor VIII protein or anywhere in the A2 or C2 domains to introduce a glycosylation site. Production of inhibitory antibodies that inactivate factor VIII is a problem in the art of treating hemophilia A by administering factor VIII. A review of the specification appears to indicate that the utility of the claimed method lies in the product that is made; a functional factor VIII molecule that evades detection by inhibitory antibodies. The invention addresses solving this problem of factor VIII inactivation by producing factor VIII molecules with glycosylation sites inserted into the epitopes of these inhibitory antibodies in order to shield the epitopes from recognition. Thus, successful practice of the claimed method involves the production of low antigenicity, low immunogenicity, and active factor VIII molecules.

10. However, Aly et al. (Proc. Natl. Acad. Sci USA, June 1992, Vol. 89, pp. 4933-4937) indicate that the introduction of glycosylation sites at certain positions of the factor VIII molecule inactivate the protein. Aly et al. teach the identification of two hemophilia patients with non-functional factor VIII proteins wherein abnormal glycosylation in the light chain and in the A2 domain blocks the factor VIII procoagulant activity (see abstract, and Discussion, p. 4936). It appears that at the time of the invention, it was surprising to find that glycosylation could affect protein function of factor VIII. Aly et al. do not propose how the glycosylation affected the procoagulant activity and the present

specification nor any other art reference at the time of the invention does not supplement this information. Thus, since one of skill in the art did not understand how glycosylation affects procoagulant activity, it would have been impossible to predict what affect a glycosylation site at a given amino acid position would have.

11. In addition to the complexity created by the lack of understanding of how additional glycosylation affects factor VIII activity, the prior art acknowledges, as evidence by Aly et al., the difficulty of understanding the effects of any particular point mutations in the factor VIII molecule due to its large size and many exons (p. 4933, Col. 1, 2nd paragraph). And, the effect of any amino acid modifications in the factor VIII sequence is unpredictable given, not only the complexity of its structure, but also its activity. Factor VIII participates in blood coagulation as an essential cofactor in the cleavage of factor X by factor IXa in the presence of $Ca^{++}$ and phospholipid. Factor VIII is produced as a single-chain protein of 2351 amino acids and is modified by proteolytic cleavages to generate amino terminal heavy chain polypeptides and a carboxy-terminal light chain. Procoagulant activity further requires thrombin cleavage of the factor VIII heavy and light chains to form a heterotrimer of subunits A1 and A1 from the heavy chain and subunit A3-C1-C2 from the light chain. Therefore, the art acknowledged unpredictability of amino acid modification on protein function especially applies to a complex molecule such as factor VIII given that the modification could affect any one of the events required for procoagulant activity. Such required events could include, for example, inhibition of one of the proteolytic cleavages due to disruption of cleavage site

or disruption of protease binding site, structural changes that prevent heterotrimer formation, or structural changes that impair formation of the enzymatic complex.

12. Despite the unpredictability of the effect of amino acid modification on factor VIII function, the specification only provides an example of successfully using the method to produce active factor VIII molecules with a specific additional glycosylation site (leucine 486 of SEQ ID NO:2 is substituted with asparagine (L486N)). The specification also suggests introducing a glycosylation site in the light chain by replacing glutamine 2189 with asparagine (Q2189N)) but does not address whether it retains its procoagulant activity. Thus, while the consensus sequence for glycosylation and recombinant means for making mutations in proteins were very well established at the time of the invention, it was not routine in the art to screen for positions within a protein's sequence where amino acid modifications (in this case both amino acid change and addition of glycosylation) can be tolerated. Obtaining both the desired functionality and structure (in this case glycosylation) of the factor VIII protein requires knowledge of and guidance as to what amino acids in the sequence are tolerant to modification and a detailed knowledge of the ways in which the factor VIII structure relates to its function (what affect does glycosylation have on activity to allow one to successfully predict what parts of the protein structure could be glycosylated while maintaining activity). Such experimentation is undue.

13. Due to the large quantity of experimentation necessary to determine what amino acid positions in the factor VIII sequence could be modified to insert a glycosylation site

that would result in an active factor VIII protein; the lack of direction/guidance presented in the specification regarding how glycosylation affects factor VIII procoagulant activity; the absence of working examples for methods of preparing a factor VIII molecule having glycosylation sites at positions other than 486; the complex nature of the invention; the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function and establishes that abnormal glycosylation blocks factor VIII procoagulant activity for undetermined reasons; and the breadth of the claims which fail to recite any structural limitations as to the position of the desired mutation, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope. To practice the instant invention in a manner consistent with the breadth of the claims would not require just a repetition of the work that is described in the instant application but a substantial inventive contribution on the part of a practitioner involving the determination of those amino acid residues in a factor VIII molecule that can be modified to successfully produce an active factor VIII with additional glycosylation. It is this additional characterization of the protein that is required in order to obtain the functional and structural data needed to permit one to produce a protein which meets both the structural and functional requirements of the instant claims that constitutes undue experimentation.

14. The examiner notes an amendment to the claims such that the first step is limited to replacing specifically leucine 486 of SEQ ID NO:2 with asparagine would overcome this rejection. The examiner also reminds Applicant that if the claim is amended to

include replacement of this specific residue position, then the amino acid replacement must be placed in context of a larger sequence (e.g. substituting leucine 486 of SEQ ID NO:2 with asparagine) in order to maintain the definiteness of the specific amino acid change.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (703) 305-3722. The examiner can normally be reached Monday and Thursday from 8 am to 5:30 pm and Tuesday and Wednesday from 9 am to 2:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at (703) 308-2923. The fax phone number for Official Papers to this Group is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Holly Schnizer, Ph.D.
December 6, 2001

Christopher S. Low

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